



Role of Liver in Heme Synthesis

By

Dr. Marwa Ali

Lecturer of Medical Biochemistry

Ain Shams university

INTENDED LEARNING OBJECTIVES (ILOs)



By the end of this lecture the student will be able to:

- 1. Outline the structure of porphyrins**
- 2. Illustrate the steps of heme synthesis**
- 3. Discuss regulatory steps of heme synthesis**

Outlines

What is Heme?

Steps of heme synthesis

Regulation of heme synthesis

What is Heme?

?What is Heme

Heme is the *colored prosthetic group* of **hemoglobin** and a number of proteins called **hemoproteins**

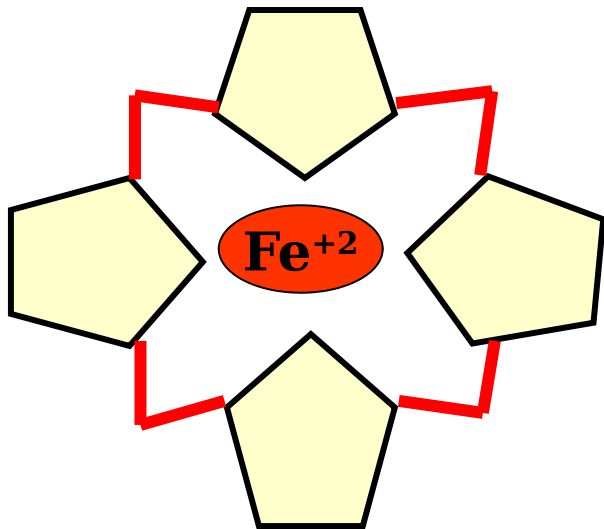
Some important heme- proteins

- **Electron transport chain cytochromes (cyt aa3, cyt.c)**
- **Cytochrome P450**
- **Catalase and Peroxidase (degradation of H₂O₂)**
- **Tryptophan pyrrolase**
- **Cytoplasmic guanylate cyclase (activated by NO)**

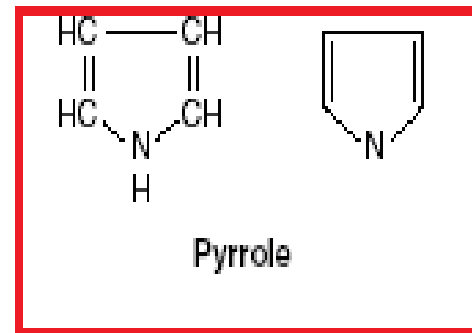
Structure Of Heme

+ porphyrin

Porphyrins = cyclic compounds formed of four pyrrole rings



Heme group



Porphyrins

They are **cyclic** compounds

formed of

4 pyrrole rings linked by **methenyl**

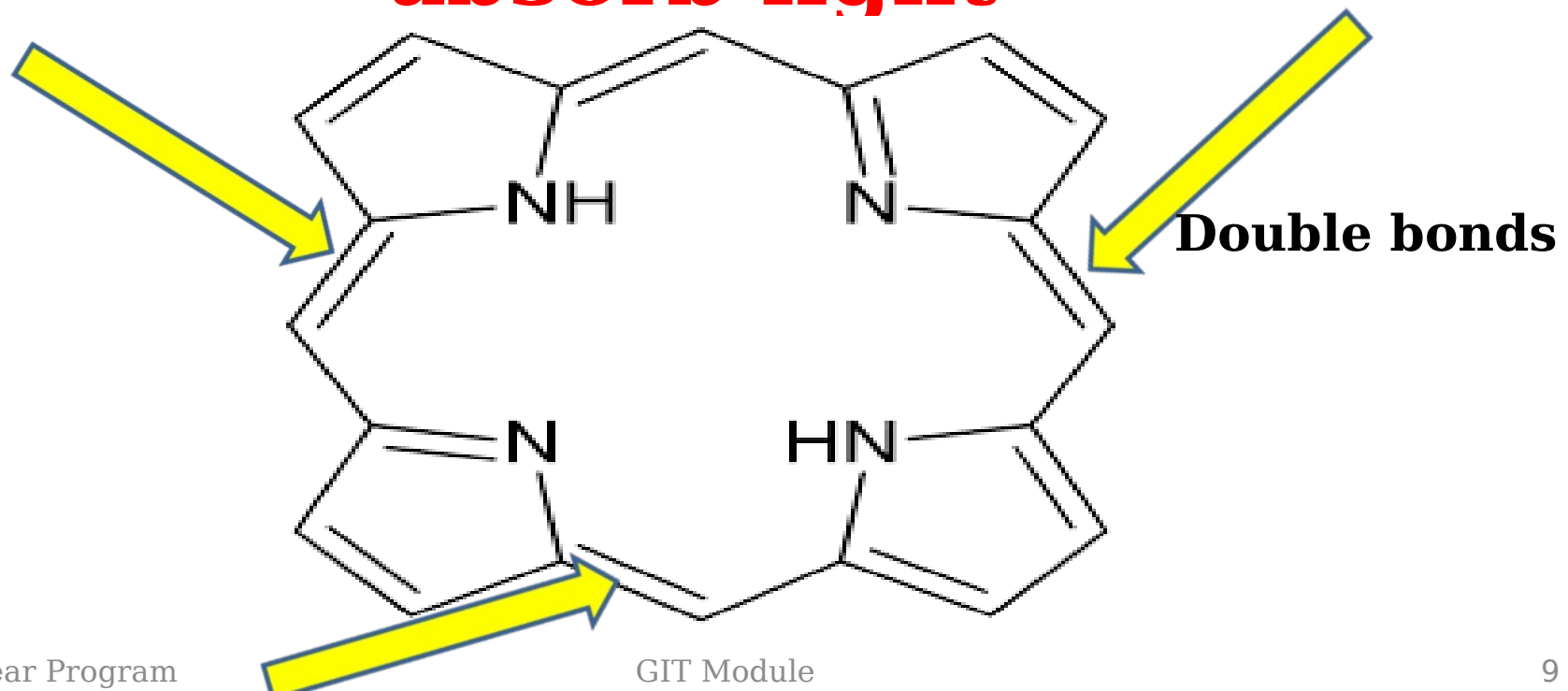
bridges.
They form **complexes** with **metal**
ions that bind to **Nitrogen** of
:pyrrole rings

,Iron porphyrins (Heme)

Magnesium porphyrins

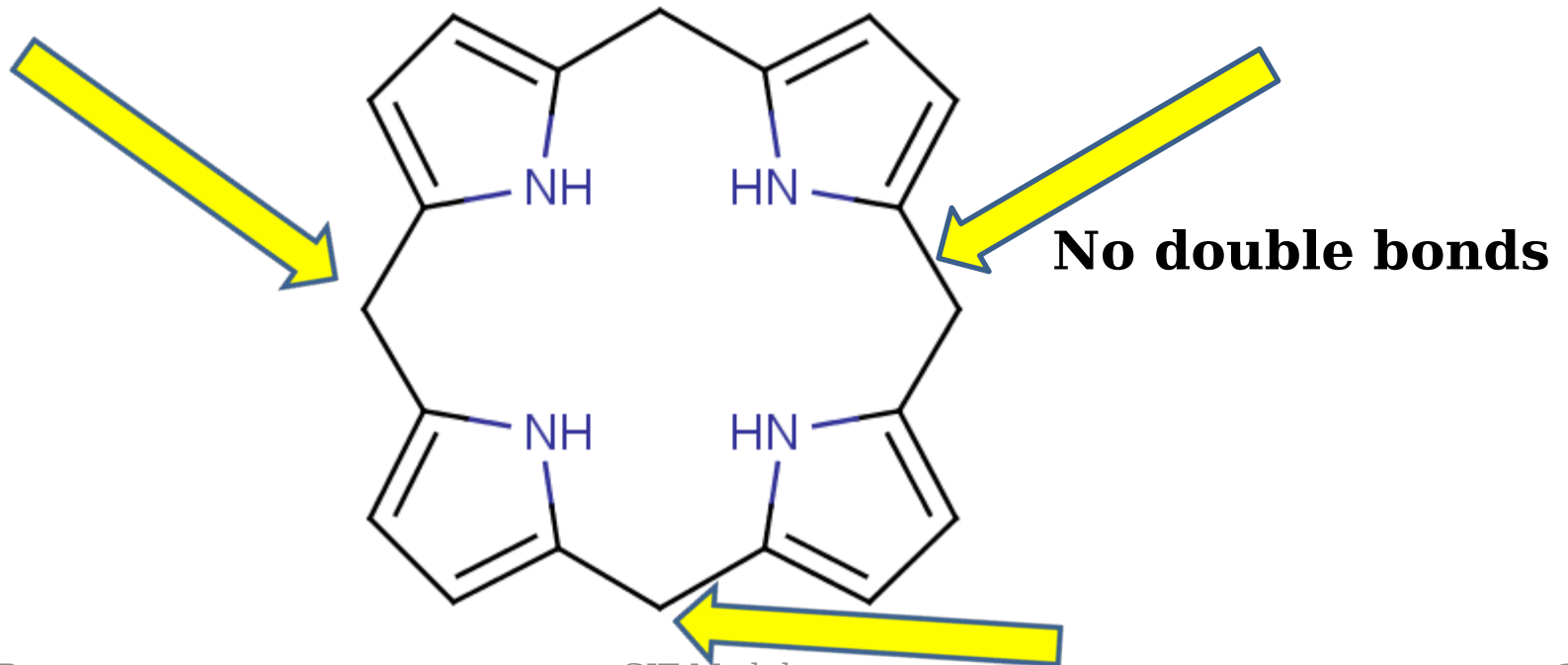
Structure Of Porphyrins

conjugated **double bonds** which
absorb light



Porphyrinogens

They are **reduced** forms of porphyrins that have **no** conjugated **double bonds** and



MCQ

**Porphyrin ring present in all of -1
:the following except**

- A. peroxidase**
- ☒ B. Xanthine oxidase**
- C. Tryptophan pyrrolase**
- D. catalase**
- E. guanylyl cyclase**

Steps of heme synthesis

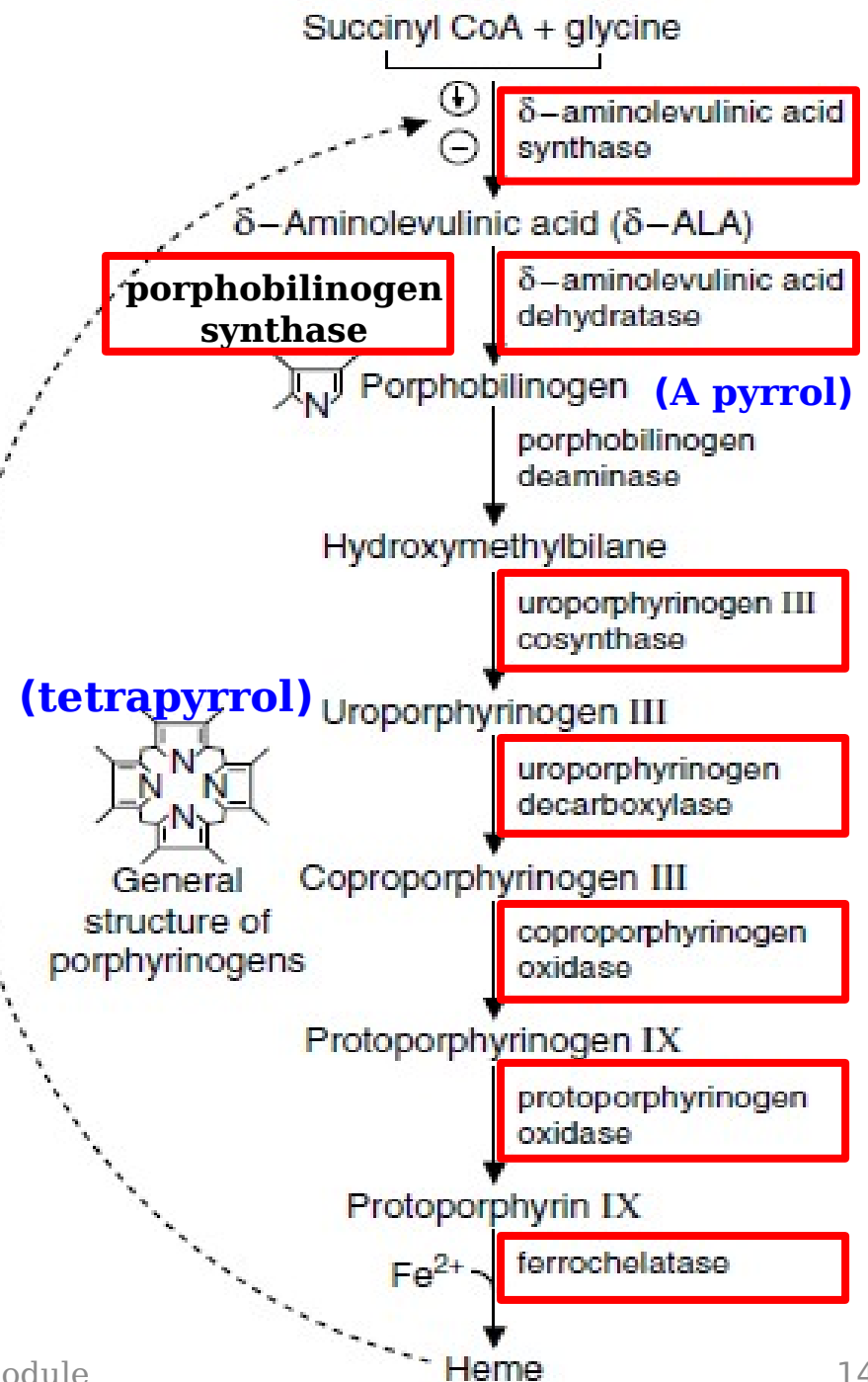
Mainly in the **bone marrow** (hemoglobin synthesis) and the **liver** (cytochrome P450 synthesis)

Heme biosynthetic pathway is partly **mitochondrial** and partly **cytosolic**

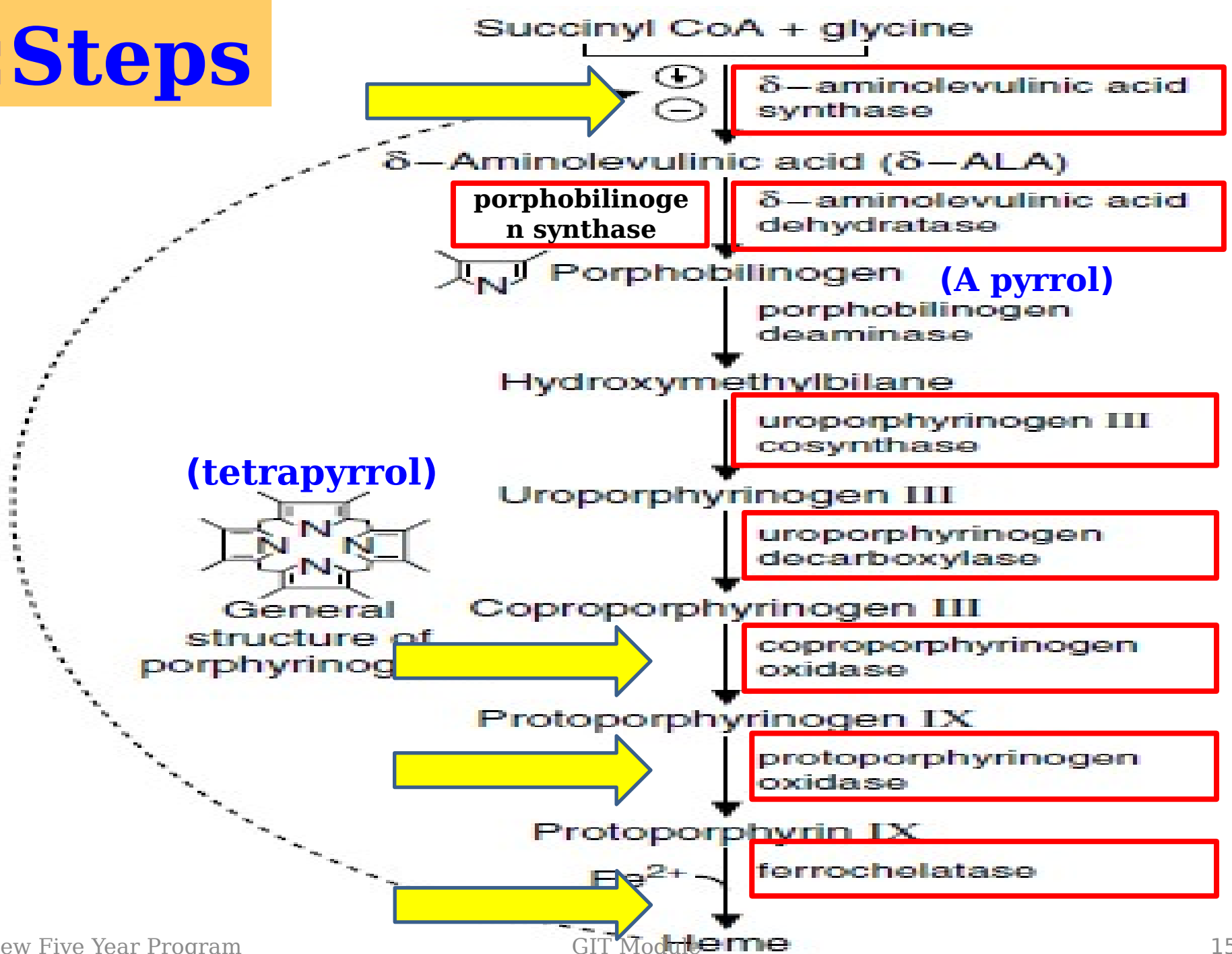
The reactions are **Irreversible**

:Steps

The **initial** reaction and the **last three** steps in the formation of porphyrins occur in **mitochondria**, but the **intermediate** steps occur in the



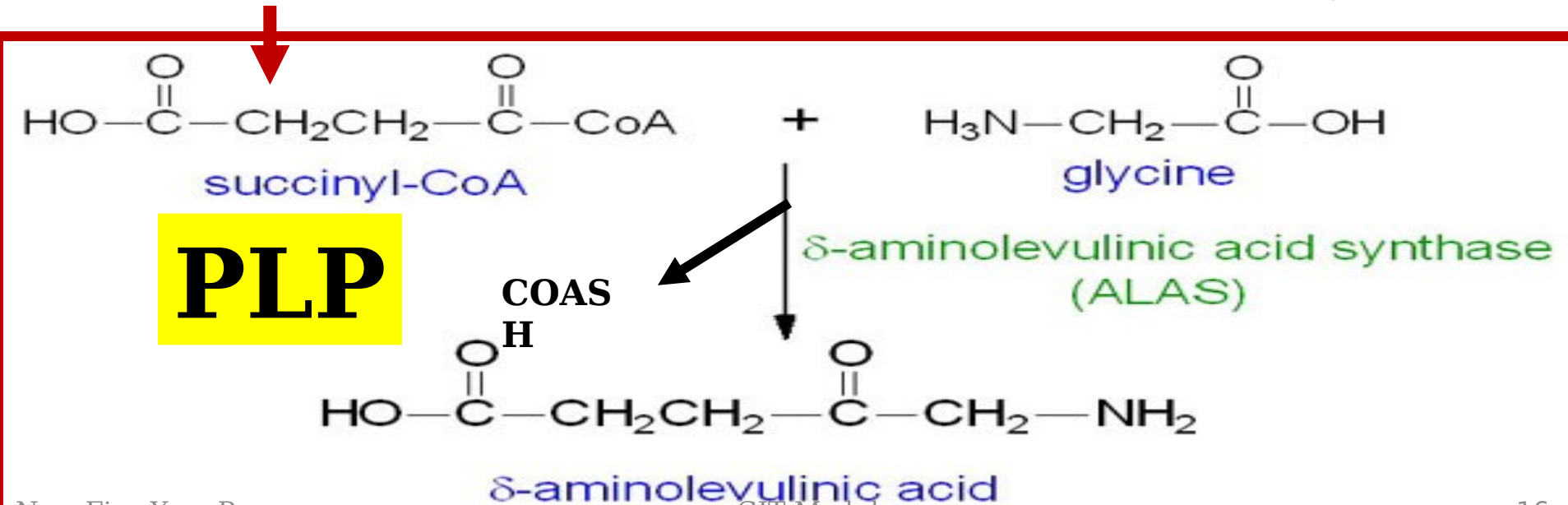
:Steps



Formation of δ -aminolevulinic acid -1 : (ALA)

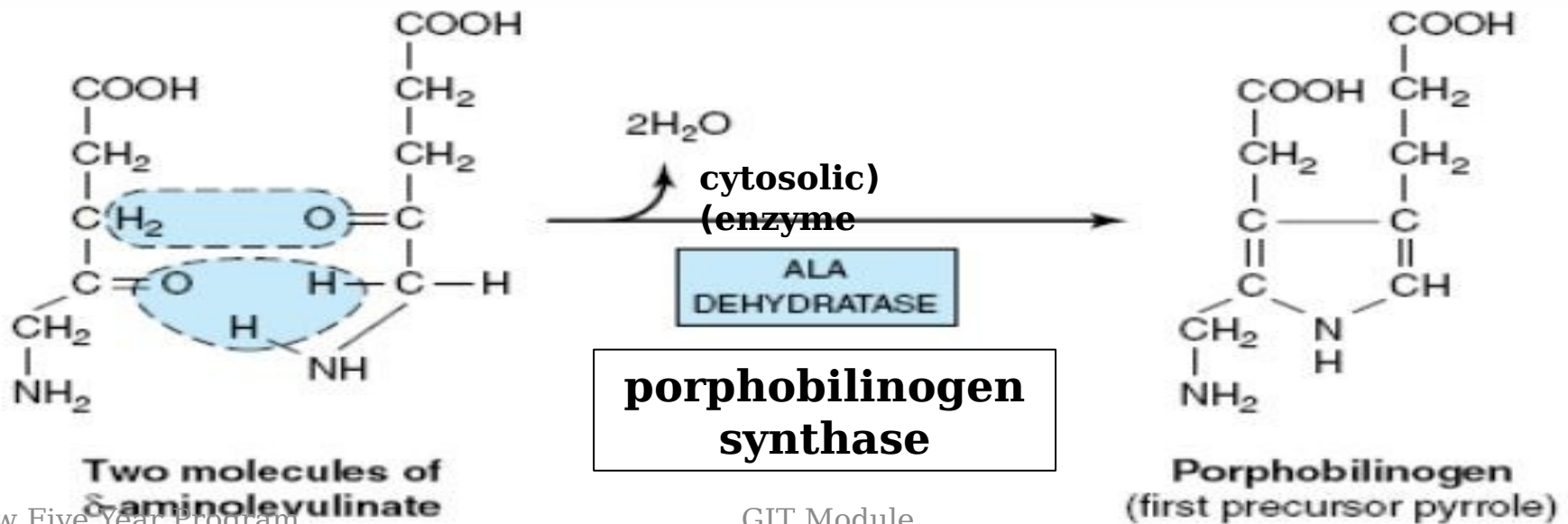
- **Glycine** and **succinyl CoA** condense to form **ALA** by mitochondrial **ALA synthase** (ALAS).

• It is the **committed step** in porphyrin



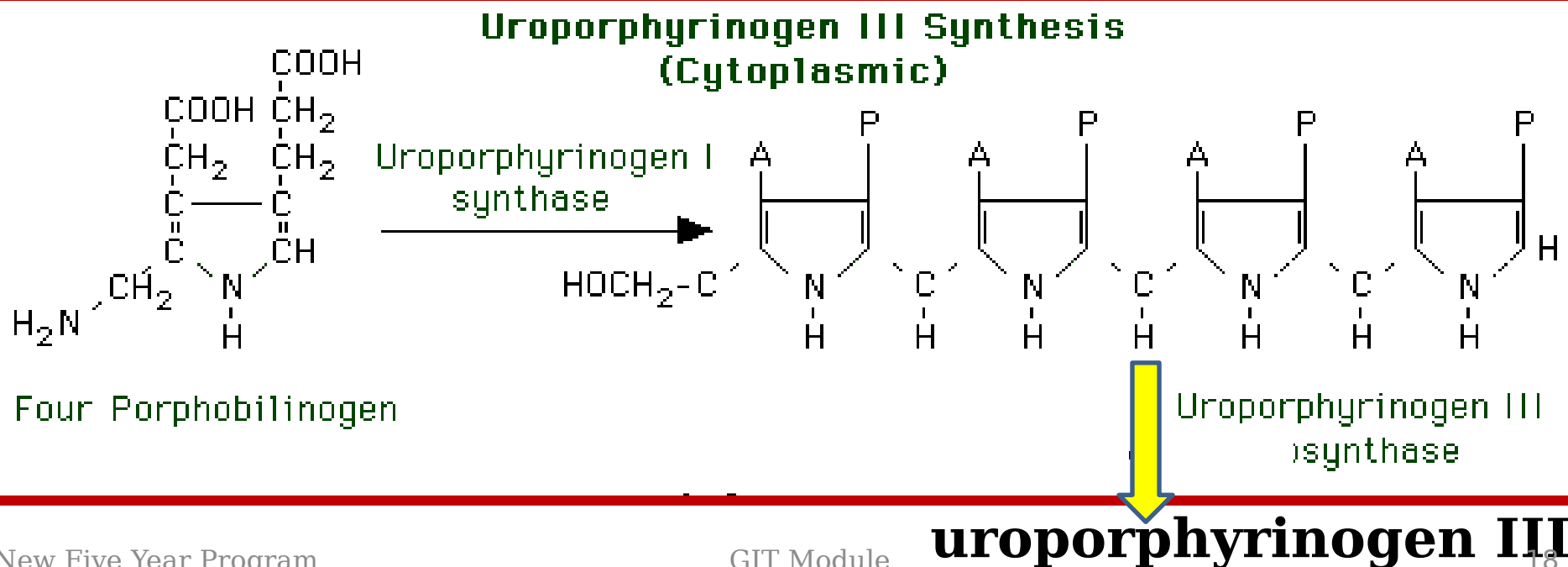
2-Formation of porphobilinogen:

- Condensation of **two** molecules of **ALA** by **Zn-containing cytosolic ALA dehydratase** (porphobilinogen synthase).
- It is **inhibited** by **heavy metal ions** e.g. **lead** that replace the zinc .



3- Formation of uroporphyrinogen:

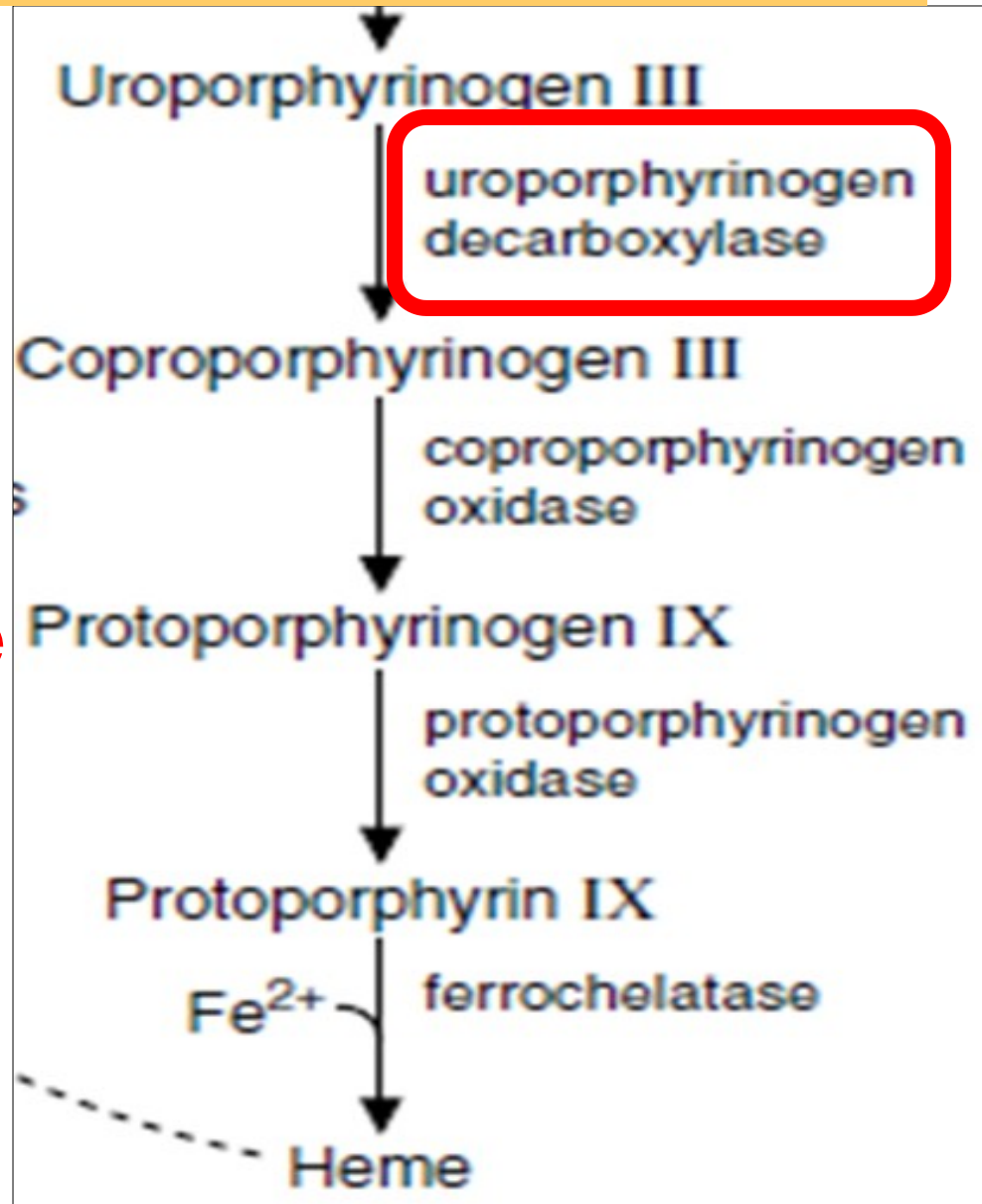
Condensation of **four** porphobilinogens produces a **linear tetrapyrrole**, which is **cyclized** forming **uroporphyrinogen III** by **uroporphyrinogen III Synthase** enzyme



4- Formation of Heme:

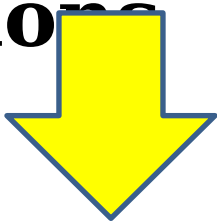
Uroporphyrinogen III undergoes decarboxylation forming coproporphyrinogen III

This reaction occurs in the cytosol

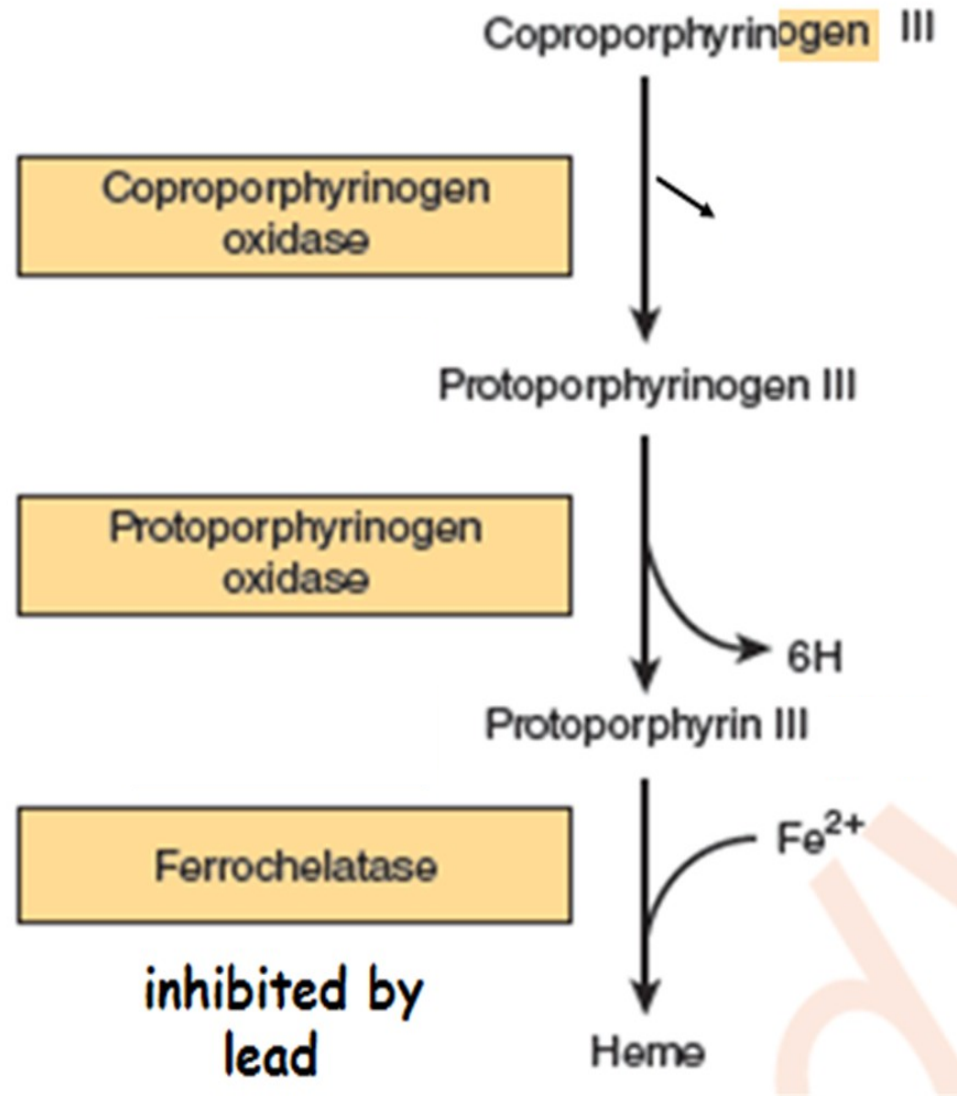


4- Formation of Heme:

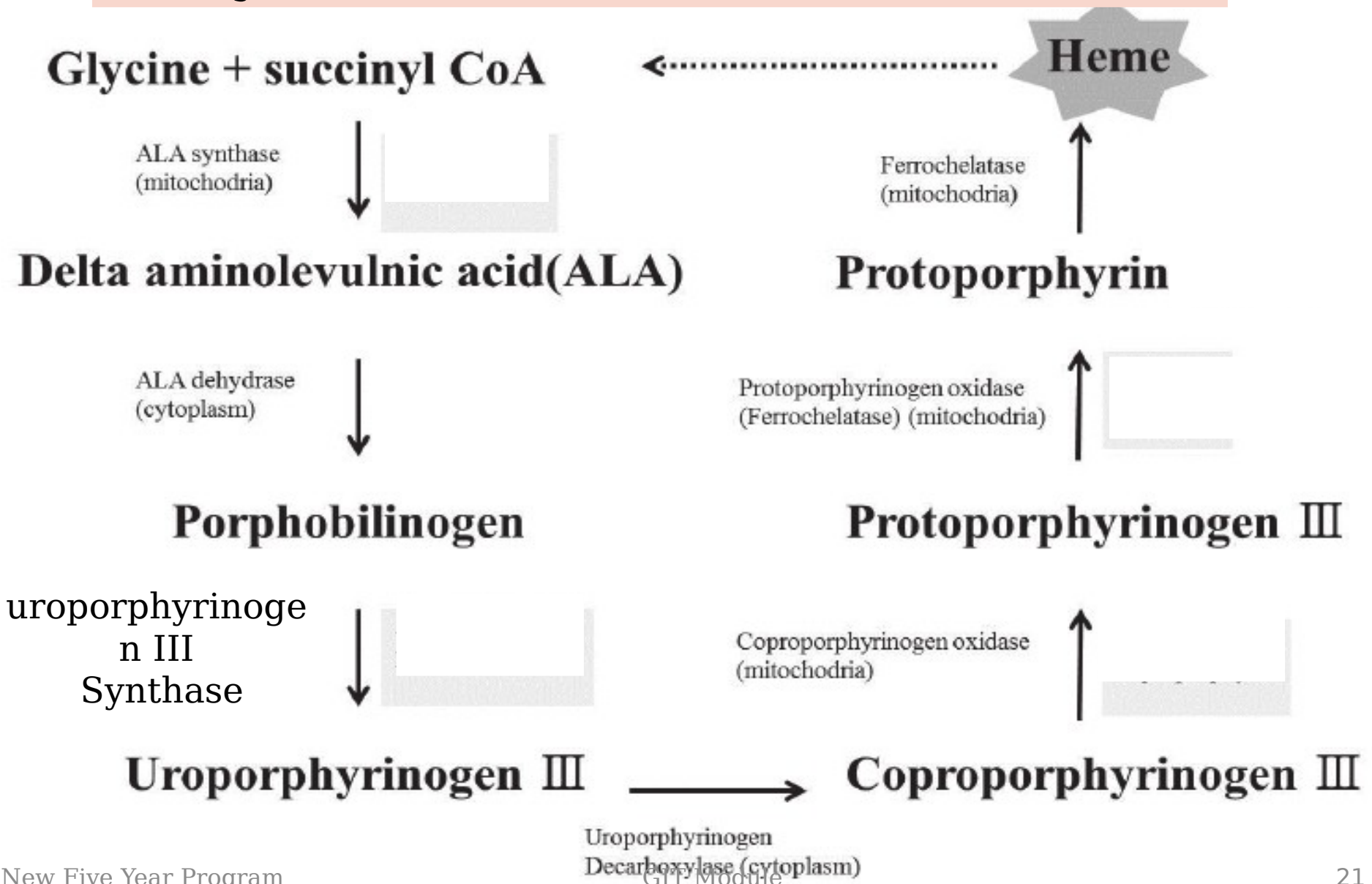
Coproporphyrinogen III enters the mitochondrion, followed by oxidation reactions.



Iron (as Fe^{2+}) is introduced into protoporphyrin by ferrochelatase enzyme.



Overall reactions of heme biosynthesis



MCQ

**An amino acid required for -2
:porphyrin synthesis is**

A. proline

B. serine

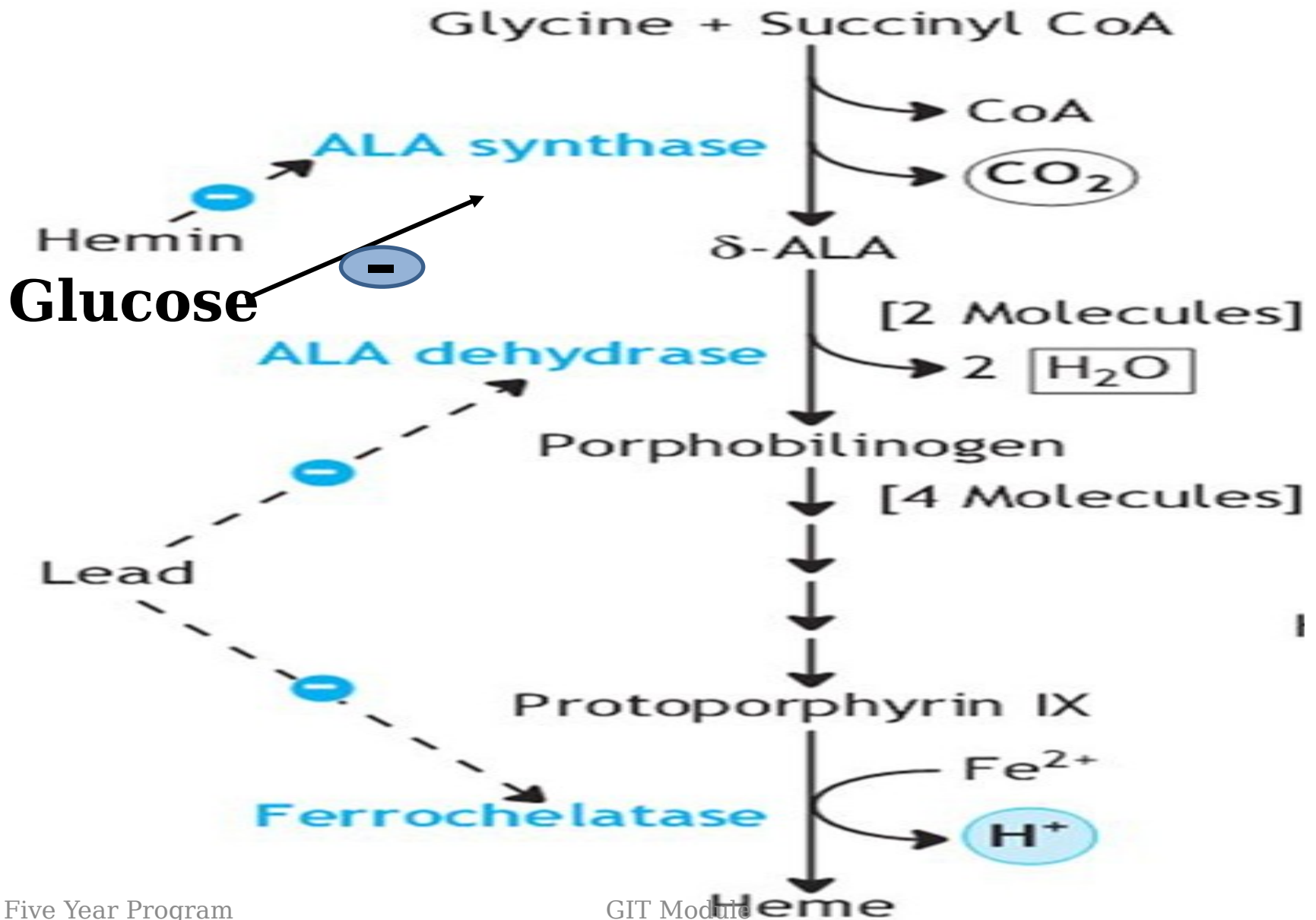
☒ C. glycine

D. histidine

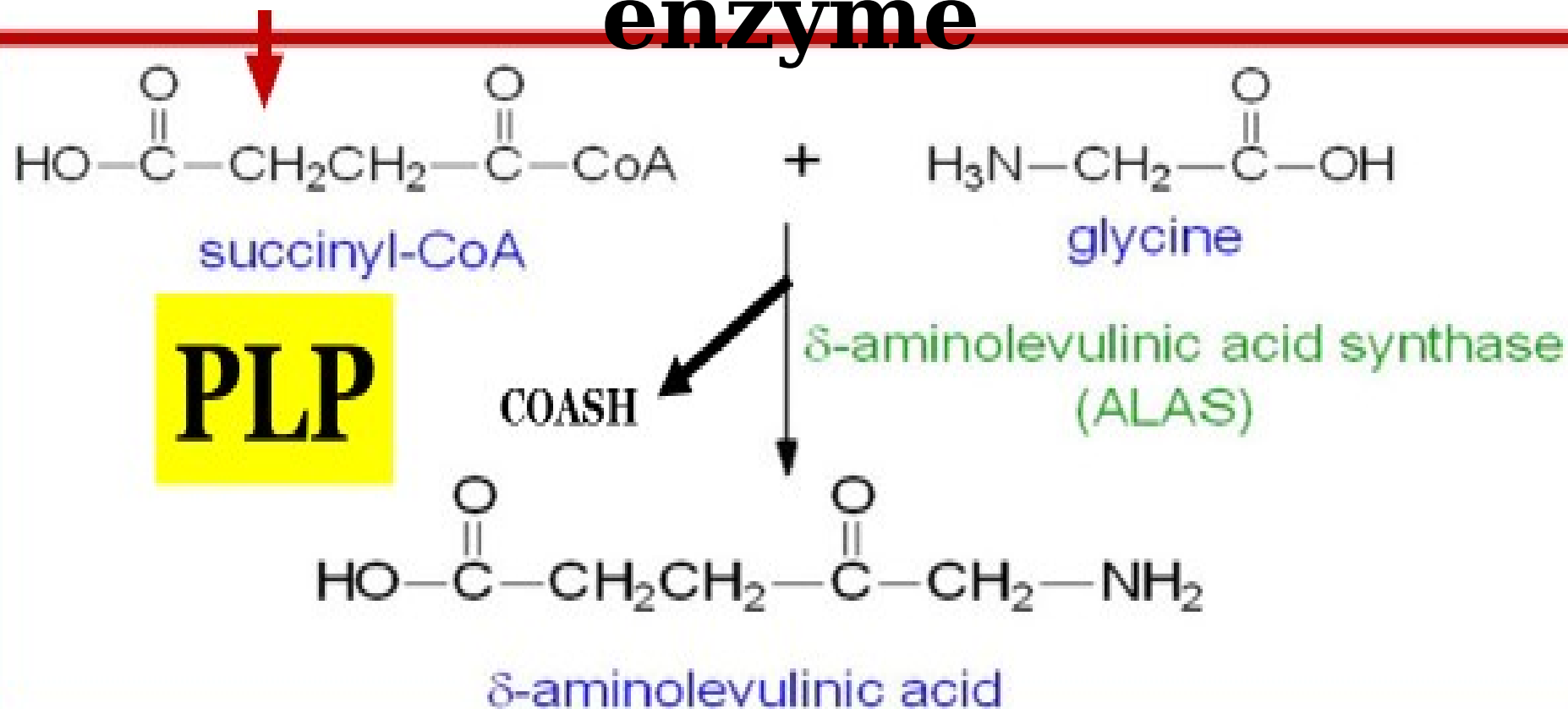
E. alanine

Regulation of heme synthesis

Regulation of Heme Synthesis



ALA synthase is the rate limiting regulatory enzyme



:Effect of heme (hemin) -1

When porphyrin production exceeds the availability of the apoproteins that require it heme accumulates and is converted to hemin by the .+oxidation of Fe^{2+} to Fe^{3+}

Hemin decreases the amount and the .activity of ALAS enzyme

Glycine + Succinyl CoA

ALA Synthase



δ aminolevulonic acid (ALA)



HEME



ALA Synthase
catalyzes first step of
heme biosynthesis
Heme end product of
the pathway act as
allosteric inhibitor

Feed Back inhibition

Effect of drugs (in liver -2 :only)

Drugs metabolized by cytochrome P450 monooxygenase in the liver .

Barbiturates
, alcohol and
carcinogens

Synthesis of cytochrome P450

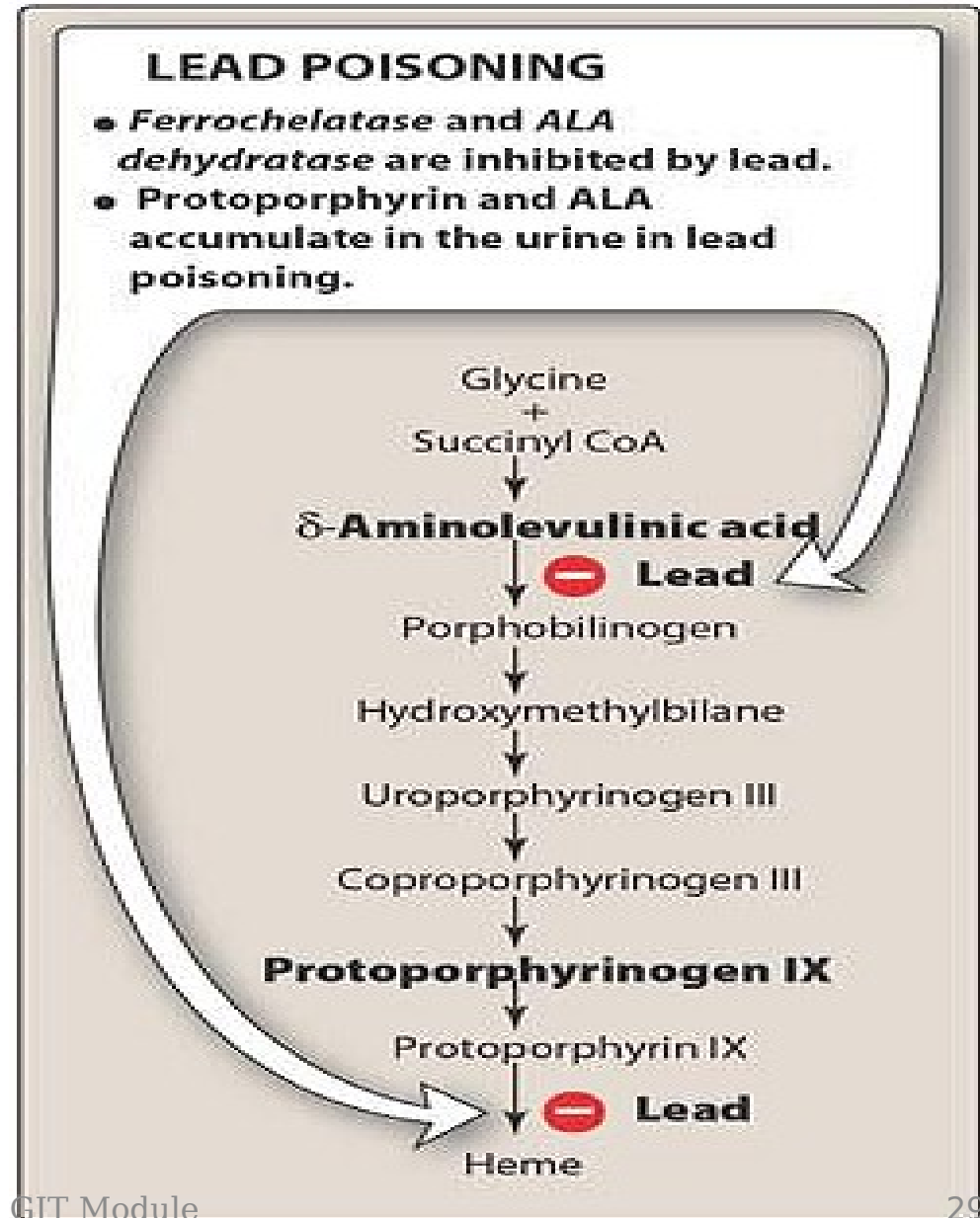
Consumption of heme
a component of cytochrome P450 proteins.

The concentration of heme in liver
Cells.

The synthesis of ALAS1 (derepression)

:Effect of Lead -3

Lead has an
inhibitory
effect on
ALA
dehydratase
&
Ferrochelatase



:Effect of Glucose -4

**Glucose has *inhibitory* effect
on ALA synthase**

MCQ

: δ -Aminolevulinic acid synthase activity -3

A. Is frequently decreased in liver in individuals treated with drugs, such as the barbiturate phenobarbital.

☒ B. Catalyzes a rate-limiting reaction in porphyrin biosynthesis.

C. Requires the coenzyme biotin.

D. Is strongly inhibited by heavy metal ions such as lead.

E. Occurs in the cytosol.

Summary

Heme = Iron in the ferrous state + porphyrin

- The initial reaction and the last three steps in the formation of porphyrins occur in mitochondria, but the intermediate steps occur in the cytosol
- ALA synthase is the rate limiting regulatory enzyme

*Thank
you*



Marwa Al